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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/449,204 11/24/99 SINICROPI

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EXAMINER

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FORMAN, B

ART UNIT

PAPER NUMBER

1655

**DATE MAILED:**

07/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

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<b>Office Action Summary</b>	Application No.	Applicant(s)	
	09/449,204	SINICROPI ET AL.	
	Examiner BJ Forman	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

- 1) Responsive to communication(s) filed on 24 November 1999.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-23 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

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**Application Papers**

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) All b) Some \* c) None of the CERTIFIED copies of the priority documents have been:

1. received.
2. received in Application No. (Series Code / Serial Number) \_\_\_\_\_.
3. received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

- |   |  |
|---|--|
| 15) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                          | 18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 16) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                 | 19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 17) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6. | 20) <input type="checkbox"/> Other: _____.                                   |

**DETAILED ACTION**

***Specification***

1. A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a) because some of the text is obliterated by the holes punched in the top of the page because the top margin is too small.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-23 are indefinite because the method steps do not achieve the claimed invention i.e. quantitating or detecting the presence of a target compound. It is suggested that Claim 1, step (d) and Claims 22 and 23, step (e) be amended at the end to recite "wherein quantitating or detecting the PCR amplified nucleic acid moiety quantitates or detects the presence of the target compound".

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b. Claims 1-23 are indefinite in step (a) of Claims 1, 22 & 23 for the recitation "capture molecule or target molecule binding fragment capable of binding to the target molecule under conditions suitable to form a capture molecule:target molecule complex" because it is unclear whether the recitation is a method step or a characteristic of the capture molecule or target molecule. The recitation is further indefinite in the recitation "suitable to form" because it is unclear whether the complex is formed. It is suggested that the claims be amended to recite positive active method steps e.g. replace "capable of binding" with "which binds" and to recite with "under conditions whereby a capture molecule:target molecule complex is formed".

c. Claims 1-23 are indefinite in Claim 1, step (d) and Claims 22 and 23, step (e) for the recitation "using a detectable non-primer probe capable of binding to the nucleic acid moiety because the "non-primer probe" lacks proper antecedent basis in the claim and because "capable of binding" is indefinite (see (b) above). It is suggested that the claims be amended to recite positive active method steps i.e. replace "capable of binding" with "which binds" and to recite a method step for probe binding.

d. Claim 10 is indefinite because the claim is improperly drawn to the target molecule of Claim 9. It is suggested that the claim be amended to depend from the protein of Claim 9 e.g. "The method of Claim 9 wherein the protein is....."

e. Claim 15 is indefinite because the claim improperly depends from Claim 7 which is drawn to a capture molecule. The claim is further indefinite in the recitation "which can quantitate" because it is unclear whether the recitation is a method step of quantitation. It is suggested that the claim be amended to depend from Claim 1, and to recite positive active method steps e.g. "The method of Claim 1, wherein the target molecule is quantitated at a concentration of  $\leq 10^{-12}$  grams/mL".

f. Claim 16 is indefinite in the recitation "which can detect the target molecule" because it is unclear whether the recitation is a method step of detection. It is suggested that the claim be amended to recite positive active method steps e.g. " The method of Claim 1 wherein the

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target molecule is detected at a concentration of about  $1.0 \times 10^{-8}$  to about  $1.0 \times 10^{-15}$ " grams/mL.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-5, 7-12, 15, 16 & 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001).

Regarding Claim 1, Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound in a sample which may contain the target compound, the method comprising: exposing the sample to a capture molecule which binds to the target molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule wherein the detector molecule binds to the target molecule to form a capture molecule-target molecule-detector molecule complex, amplifying the nucleic acid moiety by PCR amplification, and quantitating or detecting the PCR amplified nucleic acid moiety (page 523, Fig. 1). Hendrickson et al. teach the amplified nucleic acid moiety is quantitated and detected on an agarose gel by detection of moiety-specific size. Hendrickson et al. do not teach the amplified nucleic acid moiety is quantitated or detected by a detectable non-primer probe. However, detectable non-primer probes were known and routinely practiced in the art for the detection of PCR products at the time the claimed invention was made as taught by Gibson et al. (page 1000, Table 1). Specifically, Gibson et al.

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teach a method for detecting the presence of a target compound wherein the target compound is PCR amplified and detected with sequence-specific non-primer probes (page 1000, last paragraph and Table 1). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Gibson et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the size-specific detection and quantitation of Hendrickson et al. with the sequence-specific non-primer probe detection of Gibson et al. for the obvious benefit of eliminating the agarose gel step.

Regarding Claim 2, Hendrickson et al. teach the method of Claim 1 further comprising washing the capture molecule-target molecule complex to remove unbound sample after step (a) (page 525, left column, third full paragraph, lines 5-6).

Regarding Claim 3, Hendrickson et al. teach the method of Claim 1 further comprising washing the capture molecule-target molecule complex to remove unbound sample after step (b) (page 525, left column, third full paragraph, lines 11-13).

Regarding Claim 4, Hendrickson et al. teach the method of Claim 1 wherein the capture molecule is bound to a solid support (page 1372, Fig. 1).

Regarding Claim 5, Hendrickson et al. teach the method of Claim 1 wherein the capture molecule is bound to a solid support (page 1372, Fig. 1) but they do not teach the method wherein the capture molecule is in solution during step (a) or (b). However, binding of capture molecule-target molecules in solution was routinely practiced in the art. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with routinely practiced protocols to obtain the claimed invention because one skilled in the art would have been motivated with a reasonable expectation of success to modify the method of Hendrickson et al. wherein the capture molecules are immobilized with capture molecules in solution for the known benefit of

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binding capture-to-target molecules in large volumes for the obvious benefit of more rapid binding in solution as known in the art.

Regarding Claim 7, Hendrickson et al. teach the method of Claim 1 wherein the capture molecule is a DNA labeled antibody and the detector molecule is a DNA labeled antibody (page 523, Fig. 1) but they do not teach the capture molecule is a DNA labeled antibody. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to simplify the method of Hendrickson et al. to obtain the claimed invention because one skilled in the art would have been motivated with a reasonable expectation of success to label the capture molecule for single molecule capture and detection for the obvious benefit of eliminating the labeled detector molecule.

Regarding Claim 8, Hendrickson et al. teach the method of Claim 1 wherein the target molecule is an organic compound having a molecular weight of about 100 to about 1000 grams/mole i.e. human thyroid stimulating hormone (hTSH) (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 9, Hendrickson et al. teach the method of Claim 1 wherein the target molecule is a protein i.e. hTSH (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 10, Hendrickson et al. teach the method of Claim 1 wherein the target molecule is a protein i.e. hTSH (page 523, left column, second full paragraph, lines 1-3).

Regarding Claim 11, Hendrickson et al. do not teach the method wherein the sample is selected from the group consisting of blood, serum, sputum, urine, semen, cerebrospinal fluid, bronchial aspirate and organ tissue. However, Hendrickson et al. teach the method detects hTSH and therefore has utility in the detection of hTSH which is known to be present in blood (page 526, left column, last paragraph). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Hendrickson et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable

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expectation of success to apply the method of Hendrickson et al. for the expected benefit of highly sensitive detection of a target molecule in blood as taught by Hendrickson et al. (page 528, last paragraph).

Regarding Claim 12, Hendrickson teach the method of Claim 1 wherein the capture molecule is immobilized on a solid support (page 525, left column, second full paragraph, lines 1-6) but they do not teach the immobilization is via biotin labeled capture molecule bound to a streptavidin or avidin labeled support. However, biotin-labeled capture molecules immobilized via binding to a streptavidin or avidin labeled support were known and routinely practiced in the art at the time the claimed invention was made. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with routinely practiced procedures to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the immobilization of Hendrickson et al. and to immobilize the capture molecule by biotin-avidin interaction for the known benefit of rapid and specific biotin-avidin binding.

Regarding Claim 15, Hendrickson et al. teach the method of Claim 1 wherein the target molecule is quantitated at a concentration of  $\leq 10^{-12}$  grams/mL (page 527, first paragraph and Fig. 5).

Regarding Claim 16, Hendrickson et al. teach the method of Claim 1 wherein the target molecule is quantitated at a concentration of about  $10^{-8}$  grams/mL to about  $10^{-15}$  grams/mL (page 527, first paragraph and Fig. 5).

Regarding Claim 20, Hendrickson et al. teach the method of Claim 1 wherein the solid support is a 96-well thermowell microtitre plate which is placed into a thermal cycler for PCR amplification (page 525, left column, second full paragraph, lines 1-4 and fourth paragraph, lines 1-3) but they do not teach the solid support is a PCR tube. However, 96-well microtitre plates and PCR tubes were known and routinely practiced in the art for one-well/sample and

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one-tube/sample wherein reagent mixing and nucleic acid amplification for each sample is in isolation. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with routine practiced procedures to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the solid support of Hendrickson et al. wherein the solid support provides 96-wells for 96 samples based the number of samples to be assayed, available equipment and experimental design for the obvious benefit of reducing the labor and cost of 96-format assays.

6. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001) as applied to claim 1 above, and further in view of Kawazoe et al. (Biotechnology Progress, 1997, 13: 873-874). Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound in a sample, the method comprising: exposing the sample to a capture molecule which binds to the target molecule for capture molecule-target molecule binding to form a capture molecule-target molecule complex (page 523, Fig. 1), wherein the capture molecule is an antibody (page 525, left column, second full paragraph, lines 1-3). Hendrickson et al. do not teach the capture molecule is an aptamer. However, aptamers were known in the art and routinely used as capture molecules to form capture molecule-target molecule complexes as taught by Kawazoe et al. Specifically, Kawazoe et al teach a method to detect a target molecule in a sample wherein a capture molecule, which is an aptamer, binds the target molecule to form a capture molecule-target molecule complex for detection and quantitation of the target molecule (page 873, right column, last paragraph). Additionally, Kawazoe et al. teach the advantages of aptamers over antibodies as capture molecules i.e. because they are not produced by organisms which requires cell culture

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purification, they can be synthesized rapidly, reproducibly and accurately by automated processes,(page 873, left column, second paragraph). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Kawazoe et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the antibody capture molecule of Hendrickson et al. with the aptamer capture molecules of Kawazoe et al. in view of the advantages taught by the latter reference.

7. Claims 13 & 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001) as applied to claim 1 above. Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound, the method comprising: exposing the sample to a capture molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule and amplifying the nucleic acid moiety by PCR amplification (page 523, Fig. 1) wherein the amplified nucleic acid moiety is quantitated or detected on an agarose gel (page 525, right column, second full paragraph).

Regarding Claim 13, Hendrickson et al. do not teach quantitation or detection using a non-primer probe having a fluorescent dye label. However, Gibson et al. teach quantitation of the amplified nucleic acid moiety using a detectable non-primer probe having a fluorescent dye label (page 996, right column lines 1-4).

Regarding Claim 14, Gibson et al. teach the method wherein the fluorescent dye label comprises two dyes, a reporter dye and a quencher dye which fluoresce at different wavelengths (page 996, right column lines 1-16).

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Gibson et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the detection of Hendrickson et al. with the Gibson et al. method wherein the PCR reaction is detected and quantitated by fluorescently labeled non-primer probes by monitoring fluorescence emission and quenching (page 996, right column, lines 1-16) for the obvious benefit of detecting and quantitating amplified product over an extended period of time and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5).

8. Claims 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001) as applied to claim 1 above and further in view of Gold et al. (U.S. Patent No. 5,475,096, filed 10 June 1991). Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound, the method comprising: exposing the sample to a capture molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule and amplifying the nucleic acid moiety by PCR amplification (page 523, Fig. 1) wherein the nucleic acid moiety is DNA (page 523, right column, last paragraph and Fig. 2).

Regarding Claim 17, Hendrickson et al. do not teach the detector molecule is RNA and the RNA is reverse transcribed to form DNA before or during amplifying. However, Gold et al. teach a method for detecting the presence of a target molecule wherein the detector molecule is RNA and is reverse transcribed to form DNA before PCR amplification (Column 9, lines 14-40)

Regarding Claim 18, Gold et al. teach the RNA is reverse transcribed at a temperature

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sufficient to dissociate the detector molecule from the capture molecule-target molecule-detector molecule complex and reverse transcribed (Example 1, Column 36, lines 58-61).

Regarding Claim 19, Gibson et al. teach the RNA is dissociated from the complex and reverse transcribed under conditions known in the art (Example 1, Column 36, lines 62-67).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Gold et al. and Gibson et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the detector molecule of Hendrickson et al. with the RNA detector molecule of Gold et al. for the expected benefit of identifying nucleic acid ligands as taught by Gold et al. (Column 1, lines 14-31).

9. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001) as applied to claim 1 above. Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound, the method comprising: exposing the sample to a capture molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule to form a capture molecule-target molecule-detector molecule complex, amplifying the nucleic acid moiety by PCR amplification, and quantitating or detecting the PCR amplified nucleic acid moiety (page 523, Fig. 1). Hendrickson et al. do not teach quantitating the PCR amplified nucleic acid moiety using real time PCR during PCR amplification. However, real time quantitative PCR was routinely practiced in the art as exemplified by Gibson et al. (page 997, right column). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Gibson et

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al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the detection of Hendrickson et al. wherein aliquots of the PCR reaction are run on agarose gel for detection and quantitation of amplified product at one time point (page 525, right column, second full paragraph) with the Gibson et al. method wherein the PCR reaction is detected and quantitated every 8.5 seconds (page 996, left column, lines 1-3) for the obvious benefit of eliminating the agarose gel step and of detecting and quantitating amplified product over an extended period of time and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5).

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001). Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound in a sample which may contain the target compound, the method comprising: exposing the sample to a capture antibody which binds to the target molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule wherein the detector molecule binds to the target molecule to form a capture molecule-target molecule-detector molecule complex, amplifying the nucleic acid moiety by PCR amplification, and quantitating or detecting the PCR amplified nucleic acid moiety (page 523, Fig. 1). Hendrickson et al. do not teach the method wherein the amplified nucleic acid is quantitated or detected using a detectable non-primer probe and real-time PCR. However, real-time PCR and detectable non-primer probes were known and routinely practiced in the art at the time the claimed invention was made as taught by Gibson et al. Specifically, Gibson et al. teach a method for detecting a PCR amplified product with sequence-specific non-primer probes using real-time PCR (page 997, right column, page 1000, last paragraph and Table 1). It would have been *prima facie* obvious to one of ordinary skill in the

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art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Gibson et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the detection of Hendrickson et al. wherein aliquots of the PCR reaction are run on agarose gel for detection and quantitation of amplified product at one time point (page 525, right column, second full paragraph) with the Gibson et al. method wherein the PCR reaction is detected and quantitated every 8.5 seconds (page 996, left column, lines 1-3) by detection of non-primer probe hybridization for the obvious benefit of eliminating the agarose gel step and of detecting and quantitating over an extended period of time and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5). The skilled practitioner would have been further motivated to use a biotinylated aptamer and immobilize the biotinylated ternary complex with streptavidin for the known benefit of rapid isolations as routinely practiced in the art.

11. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al. (Nucleic Acids Research, 1995, 23(3): 522-529) in view of Gibson et al. (Genome Methods 1996, 6: 995-1001) and Kawazoe et al. (Biotechnology Progress, 1997, 13: 873-874). Hendrickson et al. teach a method for quantitating or detecting the presence of a target compound in a sample, the method comprising: exposing the sample to a capture molecule which binds to the target molecule to form a capture molecule-target molecule complex, adding to the complex a nucleic acid moiety containing a detector molecule wherein the detector molecule binds to the target molecule to form a capture molecule-target molecule-detector molecule complex, amplifying the nucleic acid moiety by PCR amplification, and quantitating or detecting the PCR amplified nucleic acid moiety (page 523, Fig. 1). Hendrickson et al. do not teach the method wherein the detector molecule is an RNA aptamer and the amplified RNA is

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quantitated or detected using a detectable non-primer probe and real-time PCR. However, aptamers were known in the art as taught by Kawazoe et al. and real-time PCR and detectable non-primer probes were known and routinely practiced in the art at the time the claimed invention was made as taught by Gibson et al. Specifically, Gibson et al. teach a method for detecting a PCR amplified product with sequence-specific non-primer probes using real-time PCR (page 997, right column, page 1000, last paragraph and Table 1). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teachings of Gibson et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the detection of Hendrickson et al. wherein aliquots of the PCR reaction are run on agarose gel for detection and quantitation of amplified product at one time point (page 525, right column, second full paragraph) with the Gibson et al. method wherein the PCR reaction is detected and quantitated every 8.5 seconds (page 996, left column, lines 1-3) by detection of non-primer probe hybridization for the obvious benefit of eliminating the agarose gel step and of detecting and quantitating over an extended period of time and for the expected benefit of accurate and time-saving detection as taught by Gibson et al. (page 995, right column, lines 1-5). Additionally, it would have been *prima facie* obvious to one skilled in the art at the time the claimed invention was made to modify the method of Hendrickson et al. with the teaching of Kawazoe et al. to obtain the claimed invention because one skilled in the art would have been motivated with a reasonable expectation of success to modify the detector molecule of Hendrickson et al. wherein the detector molecule is an antibody containing a nucleic acid moiety with the teaching of Kawazoe et al. who teach the advantages of aptamers over antibodies i.e. because they are not produced by organisms which requires cell culture purification, they can be synthesized rapidly, reproducibly and accurately by automated processes,(page 873, left column, second paragraph) based the aptamer's

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functionality which comprises both the antibody detector molecule's binding and in view of the advantages taught by Kawazoe et al.

### **Conclusion**

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.  
July 3, 2000

*S. Forman*  
S. Forman  
7/3/00